

(FILE 'HOME' ENTERED AT 13:33:55 ON 21 JUL 2001)

FILE 'MEDLINE, CAPLUS, EMBASE' ENTERED AT 13:34:09 ON 21 JUL 2001

L1 73 S RESTIN  
L2 10 S L1 AND ANGIOGEN?  
L3 9 DUP REMOVE L2 (1 DUPLICATE REMOVED)

L3 ANSWER 1 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.  
 ACCESSION NUMBER: 2001149119 EMBASE  
 TITLE: Endogenous **angiogenesis** inhibitors and their  
 therapeutic implications.  
 AUTHOR: Cao Y.  
 CORPORATE SOURCE: Y. Cao, Laboratory of Angiogenesis Research, Microbiology  
 and Tumor Biology Ctr., Karolinska Institute, S-171 77  
 Stockholm, Sweden. yihai.cao@mtc.ki.se  
 SOURCE: International Journal of Biochemistry and Cell Biology,  
 (2001) 33/4 (357-369).  
 Refs: 88  
 ISSN: 1357-2725 CODEN: IJBBFU  
 PUBLISHER IDENT.: S 1357-2725(01)00023-1  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 016 Cancer  
 029 Clinical Biochemistry  
 036 Health Policy, Economics and Management  
 037 Drug Literature Index

LANGUAGE: English  
 SUMMARY LANGUAGE: English

AB A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis models. While many of these **angiogenesis** inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and serpin antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of

these specific endothelial inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological **angiogenesis**, but may also provide an important therapeutic strategy for the treatment of cancer and other **angiogenesis** dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these **angiogenesis** inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic gene therapy, improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location,

and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other **angiogenesis** dependent diseases. .COPYGT. 2001 Elsevier Science Ltd.

L3 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 2000:34763 CAPLUS  
 DOCUMENT NUMBER: 132:96141  
 TITLE: Methods of inhibiting proliferative diseases by  
 inhibiting TGF.beta.-mediated **angiogenesis**  
 Sukhatme, Vikas P.  
 INVENTOR(S): Beth Israel Deaconess Medical Center, USA  
 PATENT ASSIGNEE(S): FCT Int. Appl., 78 pp.  
 SOURCE: CODEN: PIXXD2  
 DOCUMENT TYPE: Patent

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UB, ZW, AT, BE, CH, CY, DE, DK,  
ES, FI, GE, GR, IE, IT, LU, MC, NL, P, SE, BF, BJ, CF, CG,  
CI, CM, GN, GW, ML, MR, NE, SN, TD, T

AU 9950877 A1 20000124 AU 1999-50877 19990701  
PRIORITY APPLN. INFO.: US 1998-91829 P 19980706  
WO 1999-US149P1 W 19990701

AB Disclosed are methods of inhibiting proliferative diseases characterized by TGF-beta-mediated **angiogenesis** e.g. clear-cell renal carcinoma (RCC). Elevated TGF-beta.1 in RCC stimulates **angiogenesis**. Antagonizing TGF-beta. activity with neutralizing antibody against TGF-beta. provides methods of inhibiting **angiogenesis** and RCC tumor growth. It is further shown that TGF-beta.1 is target for the von Hippel-Lindau tumor suppressor protein (pVHL). Repression of TGF-beta. messages occurs predominantly at post-transcriptional level.

REFERENCE COUNT: 4

REFERENCE(S):

- (1) Ananth, S; CANCER RESEARCH 1999, V59(9), P2210  
CAPLUS
- (2) Marzo, A; CANCER RESEARCH 1997, V57(15), P3200  
CAPLUS
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EXPERIMENTAL NEUROLOGY 1997, V56(4), P435 CAPLUS
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L3 ANSWER 3 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000331436 EMBASE

TITLE: Progress in antiangiogenic gene therapy of cancer.

AUTHOR: Feldman A.L.; Libutti S.K.

CORPORATE SOURCE: Dr. S.K. Libutti, Surgery Branch, National Cancer  
Institute, National Institutes of Health, 3000 Rockville  
Pike, Bethesda, MD 20892, United States

SOURCE: Cancer, (15 Sep 2000) 89/6 (1181-1194).

Refs: 147

ISSN: 0008-543X CODEN: CANCAR

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 015 Cancer

022 Human Genetics

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB BACKGROUND. Because tumors require **angiogenesis** for growth, inhibiting **angiogenesis** is a promising strategy for treating cancer patients. Although numerous endogenous **angiogenesis** inhibitors have been discovered, the clinical evaluation of these agents has been hindered by high dose requirements, manufacturing constraints, and relative instability of the corresponding recombinant proteins. Therefore the delivery of these proteins using gene therapy has become increasingly attractive. METHODS. Based on their own antiangiogenic gene therapy research, the authors evaluated the published experience with antiangiogenic gene therapy models using the National Library of Medicine's PubMed search service and the reference lists of the publications cited. RESULTS. Greater than 40 endogenous inhibitors of **angiogenesis** have been characterized. Thirteen have been employed in gene therapy models, all of which showed antitumor activity in experimental animals. Other approaches have inhibited the expression or activity of proangiogenic cytokines such as vascular endothelial growth factor. The ideal gene delivery vector would target tumor tissue preferentially to minimize systemic toxicity of the transgene product. However, the low toxicity profile of endogenous inhibitors of **angiogenesis** has allowed the success of systemic antiangiogenic gene therapy in a number of preclinical models, in which normal host tissues act as a 'factory' to produce high circulating concentrations of antiangiogenic proteins. CONCLUSIONS. Difficulties with the large-scale use of antiangiogenic agents have hindered their investigation in clinical

trials. Antiangiogenic gene therapy offers the potential for cancer patients to manufacture their own antiangiogenic proteins. This strategy has been increasingly successful in preclinical models and represents an exciting new approach to cancer therapy. (C) 2000 American Cancer Society.

L3 ANSWER 4 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

FILE SEGMENT: 023 Urology and Nephrology  
LANGUAGE: Polish  
SUMMARY LANGUAGE: English

AB Research during the past few years has contributed vastly to a better understanding of fibrosis and **angiogenesis**. Although studies to understand the molecular processes associated with fibrosis and **angiogenesis** were performed independently of each other, some common parallels have emerged. Translation of these observations into potential therapeutic possibilities needs further exploration. (C) 2000 Lippincott Williams and Wilkins.

L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:388310 CAPLUS  
DOCUMENT NUMBER: 131:40546  
TITLE: Methods of producing anti-**angiogenic** proteins: endostatin, angiostatin or **restin**, using a Pichia yeast expression system  
INVENTOR(S): Sukhatme, Vikas P.  
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA  
SOURCE: PCT Int. Appl., 97 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929878	A2	19990617	WO 1998-US25892	19981208
WO 9929878	A3	19990916		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HP, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LF, LS, LT, LU, LV, MD, MG, MK, MN, MW, ME, NC, NE, NL, NO, PL, PT, PQ, RU, SD, SE, SG, SI, SK, SL, TC, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
FW:	GH, GM, KE, LS, MW, SD, SE, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9918065	A1	19990628	AU 1999-18065	19981208
EP 1038011	A2	20000927	EP 1998-962932	19981208
P:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
PRIORITY APPLN. INFO.:			US 1997-67883	F 19971208
			US 1998-82663	F 19980422
			US 1998-108536	P 19981116
			WO 1998-US25892	W 19981208

AB Methods for making proteins with anti-**angiogenic** properties are disclosed, including angiostatin, endostatin, and **restin**. The system used is a yeast expression system which produces biol. active proteins at high titer, specifically the Pichia pastoris yeast expression system. In particular, the pPIC2.alpha.A plasmid vector is provided which contains a multiple cloning site with a His.Tag motif. Biol. activity is evaluated by endothelial cell migration, tumor growth inhibition in mammalian systems, arrest of endothelial cell in G1 phase of the cycle cycle, and induction of apoptosis in endothelial cells. The anti-**angiogenic** proteins produced by the described methods exhibit superior biol. activity to anti-**angiogenic** proteins produced by other expression methods, and biol. active protein is typically produced at concns. of about 10-20 mg/L of culture medium.

L3 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:388268 CAPLUS  
DOCUMENT NUMBER: 131:39759  
TITLE: **Restin** and apomigren fragments of human collagen type XV .alpha.1 chain and their anti-**angiogenic** activities  
INVENTOR(S): Sukhatme, Vikas P.  
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA  
SOURCE: PCT Int. Appl., 94 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent

RW: GH, GM, KE, LS, MW, SD, SE, UG, VJ, AT, BE, CH, CY, DE, DK, ES, FI, FR, GE, GR, IE, IT, LU, MC, NL, PT, SE, BF, BG, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9918038 A1 19990623 AU 1999-18088 19981208  
 EP 1037985 A1 20000927 EP 1998-961366 19981208

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IL, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-67388 P 19971208  
 US 1998-82663 P 19980422  
 US 1998-108130 P 19981116  
 WO 1998-US26018 W 19981208

AB The invention relates to **restin**, a novel anti-**angiogenic** protein is described, as well as its fragment, designated apomigren. **Restin** is a proteolytic fragment of the C-terminal fragment of the NC10 domain of the alpha1 chain of human collagen type XV. Apomigren is a fragment of **restin**, and comprises the C-terminal 85 residues of **restin**. Methods for expression of the proteins at high titer are also described. **Restin** inhibits the migration of endothelial cells in vitro and suppresses the growth of tumors in a xenograft renal carcinoma model. Apomigren has anti-**angiogenic** activity equal or superior to that of endostatin.

REFERENCE COUNT: 6  
 REFERENCE(S): (1) Bachelot; Proceedings of the 89th Annual Meeting of the American Association for Cancer Research 1998, V39, P271  
 (2) Childrens Medical Center; WO 9715666 A 1997

CAPLUS (3) Ramchandran, P; Biochem Biophys Res Comm 1999, V255, P735 CAPLUS  
 (4) Fehr, M; J Biol Chem 1994, V269(19), P13929

CAPLUS (5) Searle, G; WO 9918899 A 1999 CAPLUS  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:388297 CAPLUS  
 DOCUMENT NUMBER: 131:41277  
 TITLE: Mutants of endostatin, "em 1" having anti-**angiogenic** activity and methods of use thereof  
 INVENTOR(S): Sukhatme, Vikas P.  
 PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA  
 SOURCE: PCT Int. Appl., 105 pp.  
 CODEN: FIMXD1  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929885	A1	19990617	WO 1998-US 6157	19981208
W: AL, AM, AT, AU, AZ, BA, BB, BG, BF, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HP, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LE, LF, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, PQ, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VE, VN, YU, ZW, AM, AZ, BY, FG, FZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SE, UG, VJ, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BG, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917180	A1	19990618	AU 1998-17180	19981208
EP 1037983	A1	20000917	EP 1998-961016	19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IL, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-67388 P 19971208  
 US 1998-82663 P 19980422  
 US 1998-108130 P 19981116  
 WO 1998-US26017 W 19981208

AB Described herein are novel mutants of endostatin, one of which, designated "EM 1", has anti-**angiogenic** activity similar or superior to that of wild type endostatin. The invention relates to the discovery of an

REFERENCE COUNT:

8

REFERENCE(S):

- (1) Boehm, T; Biochemical and Biophysical Research Communications 1998, V252, P190 CAPLUS
  - (2) Dhanabal, M; Cancer Research 1999, V59, P189 CAPLUS
  - (3) Ding, Y; Proc Natl Acad Sci USA 1998, V95, P10443 CAPLUS
  - (4) Ellenester, E; The EMBO Journal 1994, V17(6), P1686 CAPLUS
  - (5) O'Reilly, M; Cell 1997, V 90(2), P277 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

ACCESSION NUMBER: 1999:134195 CAPLUS

DOCUMENT NUMBER: 130:332418

TITLE: Antiangiogenic Activity of **Restin**, NC10

Domain of Human Collagen XV: Comparison to Endostatin

AUTHOR(S): Ramchandran, Ramani; Dhanabal, Mohanraj; Volk, Ruediger; Waterman, Matthew J. F.; Segal, Mark; Lu, Hui; Knebelmann, Bertrand; Sukhatme, Vikas P.

CORPORATE SOURCE: Penal Div., Dep. Med., Beth Israel Deaconess Med. Cent., Harvard Med. Sch., Boston, MA, 02215, USA

SOURCE: Biochem. Biophys. Res. Commun. (1999), 255(3), 735-739

CODEN: BBRCAS; ISSN: 0006-291X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Based on a homol. search with endostatin, the C-terminus 135 aa of collagen XVIII, the authors report the cloning, expression, and antiangiogenic activity of a 12 kDa human collagen XV fragment, that the authors have named **restin**. **Restin** was expressed in the prokaryotic pET expression system. The authors have shown that **restin** inhibits the migration of endothelial cells in vitro but has no effect on the proliferation of these cells. A polyclonal antibody raised against endostatin cross-reacted with **restin**. Systemic administration of **restin** suppressed the growth of tumors in a xenograft renal carcinoma model. (c) 1999 Academic Press.

REFERENCE COUNT: 13

REFERENCE(S):

- (1) Angiolillo, A; J Exp Med 1995, V182, P155 CAPLUS
  - (2) Boehm, T; Nature 1997, V390, P404 CAPLUS
  - (3) Corpet, F; Nucleic Acids Res 1998, V16, P10881 CAPLUS
  - (4) Folkman, J; Mol Med 1995, V1, P110 CAPLUS
  - (5) Folkman, J; Science 1987, V235, P442 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000035789 EMBASE

TITLE: Angiogenesis inhibitors. New anticancer strategy.

AUTHOR: Zgodzinski W.; Wallner G.; Dąbrowski A.

CORPORATE SOURCE: W. Zgodzinski, 2nd Department of General Surgery, Univ. School of Medicine in Lublin, Staszica 14, PL 20-031 Lublin, Poland

SOURCE: Polish Journal of Pharmacology, (1999) 51/6 (455-462). Refs: 47

ISSN: 1230-6002 CODEN: PJPAA3

COUNTRY: Poland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 116 Cancer  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Neovascularization has been proved to be crucial in neoplastic tumor growth

and metastases. Over the last few years, the factors that have both a positive (**angiogenic**) and negative (**antiangiogenic**) influence on tumor growth have been identified. The potential use of natural and synthetic factors that suppress vasculature formation as anticancer drugs is currently under intense investigation. Recently, several

antiangiogenic

compounds, including TNP-470 or matrix metalloproteinase inhibitors, have